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TYPE 2 DIABETES AND THE RISK OF OSTEOPOROTIC HIP FRACTURE IN

UTAH MEN AND WOMEN

by

Megan Bunch

A thesis submitted in partial fulfillment
of the requirements for the degree

of

MASTER OF SCIENCE

in

Nutrition and Food Sciences

Approved:

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ABSTRACT

Type 2 Diabetes and the Risk of Osteoporotic Hip Fracture in Utah Men and Women

by

Megan Bunch, Master of Science

Utah State University, 2006

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Department: Nutrition and Food Sciences

Prior studies have unequivocally established a consistent association between osteoporotic hip fracture risk and type 2 diabetes mellitus. One reason this association still remains unclear is primarily due to the limited amount of research conducted in this area. The Utah Study of Nutrition and Bone Health (USNBH) is a case-control study conducted in Utah during the period of 1997-2001 to determine risk factors for osteoporotic hip fracture. All study participants ($n = 2590$) were determined from Utah residents 50-90 years of age. Cases were determined from 18 Utah hospitals during 1997-2001. Age and gender-matched controls were randomly selected from the Utah Drivers License pool if less than 65 years of age and the Medicare databases if greater than 65 years of age. Logistic regression models were used to determine the association between type 2 diabetes and hip fracture risk. Logistic regression modeling controlled for gender, body mass index, smoking status,

alcohol use, physical activity, education level, and estrogen use in women. The risk of hip fracture was associated with type 2 diabetes. The significant correlation was primarily found in females in which the risk of hip fracture increased accompanying diagnosis of type 2 diabetes. Estrogen usage in females decreased ($p < 0.0001$) hip fracture risk in both former or current users. Physical activity significantly decreased the risk of hip fracture for females ($p < 0.0001$) and for males ($p = 0.001$). Smoking and alcohol use may increase the risk of hip fracture, especially in women. This study substantiates the hypothesis that type 2 diabetes mellitus increases the risk of hip fracture.

(62 pages)

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Megan Bunch

INTRODUCTION

The Utah Study of Nutrition and Bone Health (USNBH) was a case-control study conducted in Utah during the period of 1997-2001 to determine risk factors for osteoporotic hip fractures. All study participants were determined from Utah residents aged 50-90 years. The intent of this segment of the USNBH study was to verify putative factors associated with complications of type 2 diabetes mellitus and osteoporotic hip fracture.

REVIEW OF LITERATURE

Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and deterioration of bone leading to bone fragility and susceptibility to fractures (1). The 1990 Consensus Development Panel defined osteoporosis as a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and increase in fracture risk." (2).

Bone loss is a natural process of aging occurring in both genders following peak bone mass attainment. Peak bone mass is attained by approximately 25 years of age (3). Bone loss can be attributed to failure to achieve optimal peak bone mass and impaired bone formation during bone modeling processes (4). Hunter et al. (5) reported that many studies have determined marked bone loss in persons 30 to 40 years of age. Bone loss in males is approximately two-thirds that of women (5).

Beginning in the middle of the third decade, women lose approximately 35% of their cortical bone and 50% of their trabecular bone (5). During the first year of menopause, an immediate reduction in bone mass occurs due to an accelerated rate of bone loss. The increased rate lasts nearly 10 years after menopause followed by continuous age-related bone loss (5). An average reduction in bone mineral density (BMD) among postmenopausal women not receiving hormone replacement therapy for a period of 10 years has been associated with a doubling in fracture risk (2).

There is not a good explanation for bone deterioration (2). Bone tissue continuously undergoes remodeling to replace old bone tissue with new bone tissue. Bone remodeling involves mesenchymal osteoblastic activities for bone formation and hematopoietic osteoclastic activities for bone resorption (4,6). Homeostatic imbalance in the remodeling process leads to increased bone resorption and decreased bone formation. In addition, bone resorption may create weakened trabecular structures resulting in deterioration of bone tissue (2,3,6).

Osteoporosis is typically asymptomatic until a fracture occurs, although one in five women will not be diagnosed with osteoporosis even after a fracture occurs (7). As a result of the asymptomatic nature of osteoporosis, it is likely that the actual prevalence of osteoporosis is underestimated (7). Clinical diagnosis of osteoporosis is generally confirmed by low BMD. However, diagnosis of osteoporosis is also confirmed on the basis of personal history of osteoporotic fractures at any given time (2). The World Health Organization has defined low BMD as greater than 2.5 standard deviations below the mean BMD values for healthy adults 30-40 years of age (2).

Osteoporosis is the most prevalent metabolic bone disorder in the United States (3). The National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy reported that in the United States, 10 million people have osteoporosis and 18 million more have low BMD (8). The third National Health and Nutrition Examination Survey (NHANES III) reported that 34-50% of postmenopausal women have osteopenia, a decrease in calcification of density of bone, and 17-20% have osteoporosis (7). By ages 60 to 70 years, only 1 in

9 women in the United States have defined normal BMD. Moreover, 1 in 3 women have defined osteoporosis (2). The World Health Organization defines the disease state of osteopenia as having a BMD of 1 to 2.5 SDs below the young-adult mean (2). Both osteopenia and osteoporosis increase fracture risk, although osteoporosis has the greater impact (7). A 1 SD reduction in BMD may account for a 50-100% increase in nonspine fractures (5). More than half of all women and nearly one third of all men will experience an osteoporotic related fracture during their lifetime (2).

Approximately 1 in 12 men will sustain an osteoporotic related fracture in their lifetime (9). One in six Caucasian women will sustain a hip fracture during their lifetime (10,11). The incidence of hip fracture exponentially increases after 50 years of age (2,12,13). After age 50, the incidence ratio of hip fractures in women to men is approximately 2 to 1 (1). The lifetime risk of sustaining a hip fracture has been estimated at 17% for Caucasian women and 6% for Caucasian men in the United States (14). In the United States, approximately 55% of all hip fractures occur among people 80 years of age and older. Of that percentage, approximately 33% occur after the age of 85 years (2).

There are two classifications of osteoporosis, type 1 osteoporosis also referred to as menopausal and type 2 osteoporosis also referred to as senile osteoporosis (4,5,8). Type 1 osteoporosis is related to estrogen deficiency after menopause (3). Type 1 osteoporosis is typically observed in women less than 65 years of age affecting 5-25% of early post-menopausal women (5). Type 2 osteoporosis is observed in both women and men with a ratio of 2 women for every 1 man approximately 75 years of age or older (3). Once peak bone mass has been attained,

the prevalence of a bone loss pattern in type 2 osteoporosis is universally observed (5). Hip fractures are the main consequence of type 2 osteoporosis (3). The incidence of hip fractures begins to rise when men reach their late 60s and parallels the rise in women in their early 60s (15).

In 1995, the National Osteoporosis Foundation reported the annual cost of osteoporotic fractures to be about \$13.8 billion (7). This amount is expected to double over the next 25 years due to increases in the elderly population (7). The projected total cost for hip fractures in the year 2050 is \$131.5 billion (16). Half of all health care costs attributed to hip fracture patients is used for nursing home facilities (2). Nearly one third of all individuals who have sustained a hip fracture in the last year will be discharged to a nursing home (8). When men sustain a hip fracture, the mortality rate is higher than that of women (15,17,18). During the first year after sustaining a hip fracture, the mortality rate is 36% for men and 21% for women (7). Mortality after sustaining a hip fracture may be a marker of underlying disease states (19).

The majority of osteoporotic fractures in the elderly population are due to minor to moderate trauma that typically would not occur in younger adult populations. Mild to moderate trauma resulting in a fracture is defined as a fall from standing height or lower (2). Approximately 90% of the elderly population that experience a hip or wrist fracture in the United States is due to mild to moderate trauma (2).

The spine is the most common osteoporotic fracture site (2). Due to a lack of painful symptoms, only one-third of the vertebral fractures are diagnosed, and they

dramatically increase after 65 years of age (2). Whenever a vertebral fracture occurs, it is a strong indicator that additional vertebral fractures have, or will occur. It has been reported that about 50% of women 80 years or older have vertebral deformities due to previous vertebral fractures (2). Nearly half of all women with vertebral fractures have two or more deformities (2).

The annual rate of hip fractures is predicated to triple by the year 2040 (2). Functional disability greatly declines within the first year of a hip fracture (2). Reduced functionality results in increased fall rates that further exacerbate susceptibility for another hip fracture and lead to greater deterioration of physical capacity (2).

The incidence of wrist fractures substantially increases among women after menopause, but levels off after 65 years of age (2). The plateau affect observed after 65 years of age may be due to the increased rate of older women falling forward on outstretched hands (2). Women who have sustained wrist fractures have increased hip fracture risks (10).

Several known risk factors (Table 1) for osteoporosis and associated hip fracture risk include: cigarette smoking, low body weight (<127 lbs), tall stature, estrogen, deficiency, low calcium intake, excessive alcohol intake, inadequate physical activity, falls, various medications, chronic conditions, Caucasian race, age, female gender, dementia, frailty, history of fracture in first-degree relatives, and personal history of fractures (2,7,10,11,12,13). Some studies have reported lower BMD and increased risk of fractures with cigarette smoking. Increased risk of fractures also may be due to loss of low body weight increases the risk for hip

fracture (2,5,7,10,11,20,21).

Table 1. Risk Factors for Osteoporotic Hip Fractures

- Female sex
- Caucasian descent
- Increasing age
- Cigarette smoking
- Low body weight
- Tall stature
- Estrogen deficiency
- Low calcium intake
- Excessive alcohol intake
- Inadequate physical activity
- Medications (e.g. glucocorticosteroids, antiseizure medications, hormone suppressants)
- Chronic conditions (e.g. thyroid disorders, diabetes mellitus, renal disease)
- Dementia
- Frailty
- History of fractures in first degree relatives
- Personal history of fractures

Low body weight also may result in low BMD and thereby increase fracture risk (2). Low body weight has also been associated with preexisting conditions that increase fracture risk (2). Decreased adipose tissue in the body cavity may decrease endogenous estrogen activity, which then can lead to bone loss and increased fracture risk (7,20,21,22). In addition, adipose tissue surrounding the femoral hip may not provide sufficient protection in leaner people. In the event of a fall, a loss of adipose tissue can increase the risk of fracture (2,21,22). Moreover, it has been suggested that the most consistent predictor of BMD is total body fat (22,23). Hence, greater total body fat results in elevated BMD.

Tall women have an increased risk of hip fracture (10,11). The increased fracture risk may be due to a longer hip-axis (10). Tall women also have a greater distance to fall, which increases hip fracture risk (10).

Estrogen deficiency in premenopausal women or estrogen deficiency due to menopause accelerates bone loss (2,4,24,25). BMD losses of 2-4% occur up to 5 to 10 years after menopause in the absence of estrogen replacement therapy (2).

Smoking is a significant risk factor for osteoporosis and hip fracture (10,15,26). Smoking increases the risk for osteoporosis by inducing premature menopause. Smoking also causes increased metabolic breakdown of estrogen that increases bone loss (5). Estrogen breakdown increases bone remodeling and osteoclastic activity (27). Orwoll et al. (28) reported smoking in men 60 years of age and older was associated with lower BMD (28).

Excessive alcohol intake is a strong risk factor for bone loss and fractures (2,15). Excessive alcohol intake may impair osteoblastic activity. Furthermore, high consumption of alcohol may lead to protein and/or calcium malnutrition, reduced mobility, and hypogonadism (5). Chronic alcohol use may increase fracture risk due to increased fall rates and hepatic disease (2). Hepatic encephalopathy, resulting in decreased cognitive ability, may lead to increased fall rates as a result of decreased functionality and cognitive capacity.

Sedentary living is a strong risk factor for bone loss and fractures (2,7,10,22). Physical activity, in particular bone building exercises, help to maintain or possibly increase BMD and thereby reduce fracture risk (29,30). Epidemiological studies have suggested that hip fracture risk decreases by 20% to 50% for physically active adults

compared to sedentary adults in the United States (31). Even after attainment of peak bone mass, bone tissue can adapt to mechanical loading promoting bone remodeling. If physical activity is absent, then reduction in bone mass often ensues (30,31). Other possible benefits of physical activity may include improved agility and coordination, as well as increased muscle strength that may lower the likelihood of experiencing a fall, and therefore reducing fracture risk (2,29,30,32).

Increased fall rates may largely affect hip fracture risk rather than vertebral fracture risk (2). Vertebral fractures primarily occur spontaneously from bone deterioration and low BMD, combined with minimal trauma of low impact forces such as bending or lifting (2). Fall mechanics may play a role in the etiology of hip fracture. Falls to the side with impact to the hip or side of the leg increases hip fracture risk (33).

African American women, Hispanic women, and Asian women have a lower fall incidence compared to Caucasian women (1,2). Nearly 20% of Caucasian women 60-64 years of age and 30% of Caucasian women 80-84 years of age fall annually (2). Hip fractures occur twice as often in Caucasian women compared to African American, Asian, and Hispanic women (2). It appears however, that of the Hispanic subgroup populations, Mexican Americans have the highest hip fracture risk although hip fracture incidence rate is lower than Caucasians (34). The lower hip fracture incidence in African Americans may be due to overall high BMD levels (2). Lower hip fracture risk in the Japanese populations is most likely related to lower fall rates as well as different femoral hip geometry compared to other populations (2).

Long-term usage of corticosteroids may result in decreased BMD and increased fracture risk (2). Fitzpatrick (35) reported that BMD is reduced 40-60% in patients with endogenous glucocorticoid excess and pathologic fractures have been observed in 16-67% of the patients (35). In addition, hip fracture risk doubled in the glucocorticoid treated patients (35). Glucocorticoid induced bone resorption may also be in part due to secondary hyperparathyroidism and hypogonadism (15,35). Long-term elevation of parathyroid hormone (PTH) levels increases osteoclast bone resorption (35,36). Furthermore, glucocorticoid therapy inhibits insulin-like growth factor (IGF) synthesis. IGF-1 is synthesized by bone cells and stimulates bone cell replication and collagen synthesis (35,37,38). Glucocorticoids may also affect IGF-binding proteins leading to inhibition of IGF activity. Glucocorticoid therapy may give an overall effect to reduce bone formation by decreasing IGF-binding protein 3, IGF-binding protein 4, and IGF-binding protein 5 (35).

Anticonvulsants and other medications may also contribute to bone loss. Drug interactions and the conditions for which certain drugs are prescribed also impact bone mass (2). Bone disease associated with convulsant therapy may lead to high-turnover osteoporosis. Furthermore, seizure episodes may increase hip fracture risk (35).

Chronic health conditions contribute to poor bone health. Low body weight is a strong risk factor for hip fractures and may be a consequence of chronic disease (2,3,10,11). Several disease states associated with bone loss and fracture incidence include hypogonadism, renal disease, dementia and cognitive impairment, cardiovascular disease, diabetes mellitus, stroke, hyperthyroidism, and

hyperparathyroidism (2,3,39). Both hyperthyroidism and hyperparathyroidism can stimulate bone formation as well as bone resorption (4,35,36). Consequently, if osteoblastic cells are not significantly responsive, bone loss may occur. Ahmed et al. (12) reported increased fracture risk in women with hypothyroidism or hyperthyroidism (12). Secondary hyperparathyroidism can be caused by intestinal malabsorption and renal disease associated with vitamin D metabolism impairment (15,36,40,41).

PTH levels increases with age and is present in higher concentrations in the elderly and those persons who have previously sustained hip fractures. Increased PTH levels may result in increased bone turnover (40,42). Furthermore, low serum 25-hydroxyvitamin D levels are often observed in the elderly population are often associated with high serum PTH levels. Higher levels may accelerate bone loss and thereby increase hip fracture risk (36).

Aluminum induced osteomalacia may be observed in hemodialysis patients (35). Aluminum inhibits bone mineralization and phosphate absorption. Aluminum induced osteomalacia may increase serum phosphate levels and lower 1,25-dihydroxyvitamin D levels (35).

Cummings et al. (10) reported that a woman, whose mother sustained a hip fracture, especially before 80 years of age, doubled the likelihood of sustaining a hip fracture during her lifetime compared to controls (10). The increased hip fracture risk was independent of BMD, weight, and height (10).

It has been reported that genetics accounts for 50-60% of peak bone mass (15,17). Seeman (27) reported that twin studies and family member studies have

found that differences in bone size, shape, and BMD of individuals of the same age are likely due to genetic rather than environmental differences, although no genes have been consistently shown to account for the differences (1,27). It has been suggested that several genes rather than one or two genes with major effects account for bone mass regulation (1). Seeman (27) stated that the inconsistencies may be due to poorly defined phenotypes, and that fractures are too rare to define an association of genes to bone size, shape, and BMD (27).

Fractures have been associated with lower BMD (28). And, a previous history of fractures has been associated with an increased risk for future fractures (2,41,43). Adults who sustain a fracture, are 50% to 100% more likely to sustain a subsequent fracture (14). The risk of a future fracture increases 2 to 3 times for each previous fracture (2). Ross (2) stated that among women greater than 80 years of age who had a history of wrist fractures, 30% of those women subsequently experienced a hip fracture during their lifetime (2).

Diabetes Mellitus

Diabetes mellitus is defined as a heterogeneous group of conditions represented by increased serum glucose concentrations, carbohydrate, fat, and protein metabolism abnormalities, and the propensity to develop marked, specific forms of renal, ocular, neurologic, and premature cardiovascular diseases (44,45,46). The exact pathogenesis and etiology of diabetes mellitus is not known (44,45,46). Conditional diagnosis of diabetes is made with a normal fasting plasma glucose

(FPG) level greater than 7.0 mmol/L (126 mg/dL) (44,45,46,47). It is recommended that FPG be tested different days to confirm diagnosis of diabetes (44,45,46).

Although the classification of diabetes type may be unclear due to definition over-lap, it falls into several general types: type 1 diabetes and idiopathic type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types of diabetes that are considered primarily risk factors for another diabetes type (46).

Type 1 diabetes is an immunologically mediated and genetically linked disorder (41). Genetic predisposition to type 1 diabetes is strongly associated with *HLA-DQ* and *DR* on the short arm of chromosome 6 (45). Furthermore, the insulin gene on chromosome 11 and the cytotoxic T-lymphocyte antigen gene on chromosome 2 may be associated with type 1 diabetes (44,45). Approximately 60% of the genetic susceptibility to type 1 diabetes is thought to be related to *HLA* genes (46). However, at least 11 other loci have been reported to be involved, with nearly 10% of the genetic predisposition being accounted for by the flanking region of the insulin gene on chromosome 11 (45).

The pathogenesis of type 1 diabetes may result from autoimmunity reflected by autoimmunity reflected by autoantibodies against insulin (44). Approximately 90-95% of type 1 diabetics have antibodies against one or more pancreatic beta cell islet components (45). Moreover, 3.5-4% of first-degree relatives without type 1 diabetes also have circulating antibodies (45). The pathophysiology behind type 1 diabetes involves total destruction of the pancreatic beta cells resulting in complete dependence on exogenous insulin (44).

Type 1 diabetes usually occurs before 30 years of age (44,45). The annual incidence rate of type 1 diabetes is 18.2 cases/100,000 people under the age of 20 (45). Incidence rate is lower in African Americans, Hispanics, Asian Americans, and American Indians as compared to Caucasians (45). The annual prevalence rate of type 1 diabetes is 1 case/590 people under the age of 20 (45). Approximately 5-10% of people with diabetes have type 1 diabetes (44,45,46). The clinical signs and symptoms identified in type 1 diabetics prior to the presentation of type 1 diabetes include: polyuria, polydipsia, fatigue, polyphagia, blurred vision, persistent hyperglycemia, dehydration, ketoacidosis, significant weight loss, irritability, and fatigue (45).

Type 2 diabetes is the most common type of diabetes and accounts for about 90% of diabetic patients in the United States (44,45,46). Type 2 diabetes is a heterogeneous disease of unknown etiology primarily manifested through environmental factors that may interact with susceptibility genes (45,46). Genetic susceptibility to type 2 diabetes is enhanced through environmental factors such as sedentary living and obesity (45,46). A type 2 diabetic with polygenic defects are manifested via insulin deficiency, impaired beta cell insulin secretion, and visceral obesity (45). The development of type 2 diabetes involves reduced cellular insulin secretion, diminished liver, muscle, and adipose tissue sensitivity to insulin, and impaired insulin action that cannot compensate for increased serum glucose concentrations (45,46,48).

Type 2 diabetes is multifactorial and requires both environmental and genetic factors (46,49). A type 2 diabetic phenotype can develop in persons with normal

insulin sensitivity who have a monogenic defect that impairs beta cell function or in persons who have one of several polygenic defects in which obesity, insulin resistance, and impaired beta cell insulin secretion are all part of the altered metabolic state (49). Approximately 85% of the diabetic population has polygenic defects (49). Moreover, environmental conditions can influence both monogenic and polygenic defects (49).

A treatment regimen to control serum glucose levels must be administered (45,46). Personalized treatment will depend on the age of the patient, years of anticipated survival, other health conditions, and the compliance of the patient to specific treatment regimens (45,46). Diet therapy alone or concomitantly used with oral pharmacological agents may be used as treatment to reduce hyperglycemia (45,46). Over time, total exogenous insulin dependence may result (46). Although type 2 diabetes can occur at any age, type 2 diabetes has been observed increasingly among children as a consequence of the emerging epidemic of childhood obesity (46).

Worldwide, the prevalence of diabetes is estimated to double within the next 25 years and will affect approximately 300 million people by the year 2025 (46). More than 80% of the estimated 300 million people will suffer from type 2 diabetes (46). Chronic diabetes often leads to serious medical complications. Retinopathy, nephropathy, and neuropathy are long-term complications of diabetes and may be indicators of diabetes severity and poor glycemic control (44,45,46).

Retinopathy affects greater than 6 out of 10 type 1 diabetics (46). It is estimated that 70-100% of type 1 diabetics acquire retinopathy (50). In addition, 60%

of type 2 diabetics experience some degree of retinopathy (51). Retinopathy is normally observed in type 2 diabetics having the disease for more than 20 years (44,46). There are two types of retinopathy associated with diabetes: nonproliferative and proliferative (46,51). Nonproliferative is considered a mild form of retinopathy and is also the most common form of retinopathy. Nonproliferative retinopathy occurs when blood vessels in the retina become weak and swelling resulting in bulging or fatty deposition of the vessels (46). Nonproliferative retinopathy does not cause visual disturbances unless associated with macular edema (44,45). Proliferative retinopathy occurs when blood vessels in the retina become damaged resulting in bleeding and closing off of microaneurysms and hard exudates (44,45,46). Moreover, the retina may compensate with new blood vessels, or they may in turn bleed. If heavy bleeding results or if bleeding occurs in certain areas of the eye, vision may be altered or impaired. New blood vessels can also form scar tissue that can push or pull on the retina distorting vision (46).

The diabetic person is twenty times more likely to develop nephropathy than a person without diabetes (46). Greater than 3 out of 10 people with type 1 diabetes and nearly 1 in 10 people with type 2 diabetes will experience nephropathy (46). Nephropathy is characterized by proteinuria, hypertension, edema, and renal insufficiency (45). Nephropathy can lead to kidney failure. In the United States, diabetes is the leading cause of kidney failure (46). Kidney failure is four times more common in African Americans with diabetes than in Caucasians with diabetes (46). In addition, kidney failure is four to six times more common in Hispanics and six times more common in American Indians with diabetes than in Caucasians with

diabetes (46). It may be that African Americans, Hispanics, and American Indians experience kidney failure secondary to diabetes at a higher ratio than Caucasian Americans, due to the higher prevalence rate of diabetes (46). Approximately 40% of people beginning dialysis in the United States has diabetes (45). Of that percentage group, half have type 1 diabetes (45).

Diabetes is an independent risk factor for peripheral neuropathy (52). High serum glucose levels can damage nerves by weakening capillary walls that nourish nerves, which then can lead to neuropathy (46). Depending on the degree and severity of neuropathy, gastroparesis, peripheral neuropathy, and urinary incontinence and dysfunction secondary to a neurogenic bladder, etc. can occur (44,46). Sensory nerve damage of the feet may lead to loss of sensation in the feet, which then may lead to ulcerations and infections of the feet. In addition, high serum glucose levels can reduce blood circulation to the feet by arterial constriction and vascular insufficiency thus impairing wound healing. If ulcerations of the feet are left untreated, foot amputations often result (44,45,46). Approximately 60,000 foot amputations are performed annually in the United States (46).

Other complications of diabetes resulting from blood vessel damage are coronary artery disease and stroke (44,46,52,53,54). Type 2 diabetes is an independent risk factor for macrovascular disease (44,55). Vessel damage incurred by high serum glucose levels increases the risk for arterial plaque formation. Vessel damage also increases arterial pressure leading to reduced blood circulation (44,46). Coronary heart disease alone is the direct cause of 77,000 deaths annually in the United States among people with diabetes (46). Cerebrovascular accidents affect

400,000 people in the United States annually. Of which, 25% do not survive the incident (52).

Although the exact etiology of the pathogenesis of type 1 diabetes and type 2 diabetes is unclear, there are several factors that increase risk of developing diabetes. The chance of acquiring type 1 diabetes or type 2 diabetes increases if a family member has type 1 diabetes or type 2 diabetes (45,46). For example, if one identical twin develops diabetes, the likelihood of the other twin developing diabetes is 25-50% (45). This risk of developing diabetes for the other twin is in contrast to a 0.4% risk in the general population, a 15% risk to a human leukocyte antigen (*HLA*) identical sibling, and a 1% risk in an *HLA* nonidentical sibling (45).

Excess body weight is a strong risk factor for developing type 2 diabetes (32,45,46,56,57). Greater than 8 out of 10 persons with type 2 diabetes are considered overweight (46). The higher the proportion of fatty tissue in the body, the greater the resistance to insulin muscle and tissue cells experience (46,58). Moreover the insulin resistance phenomenon is increased when excess visceral fatty tissue is concentrated in the abdomen area (46,58). However, persons with type 2 diabetes can improve serum glucose levels by moderate weight loss (46).

Sedentary living is considered a risk factor for type 2 diabetes (32,46,56). About 70% of adults in the United States either do not engage in any physically activity or are considered sedentary (59). Physical activity aids in maintaining appropriate body weights, utilizing serum glucose in the form of energy, sensitizing muscle and tissue cells to insulin, increasing blood flow and vessel circulation, and increasing muscle mass (32,46). In normal conditions, approximately 70-90% of

serum glucose is absorbed in muscle tissue (46). Consequently, lack of physical activity may lead to reduced muscle mass and hence, impaired serum glucose absorption in muscle tissue. Physical activity, independent of obesity, has been shown to decrease the risk for type 2 diabetes (59).

The likelihood of acquiring type 2 diabetes increases with age. Most notably, after the age of 45, the risk of developing type 2 diabetes increases (46). It is estimated that 1 in 5 Americans older than 65 years of age have type 2 diabetes (46). The increased risk of developing type 2 diabetes as people age may be partly due to less engagement in physical activity and hence, less muscle mass, and weight gain (46).

Type 2 diabetes is more apparent in Hispanic, African American, and American Indian populations in the United States (44). Furthermore, type 1 diabetes is more common in Caucasians in the United States as well as in European countries (45,46). The etiology of ethnicity and risk for developing diabetes is unclear (46). It may be that the etiology of ethnicity and diabetes is multifactorial.

Diabetes Mellitus and Osteoporotic Hip Fractures

Prior studies have not established a consistent association between osteoporotic hip fracture risk and diabetes mellitus (60). One reason for this is the limited amount of research conducted in this area. Until more data is gathered, debate will continue on the association between diabetes and osteoporotic hip fractures. One possible reason for lack of association is insufficient data on bone mineral density (BMD) and the risk of osteoporosis in type 1 and type 2 diabetic patients (61). Due to

pathogenic differences in the onset and physiology of type 1 and type 2 diabetes, BMD status has often, but not always, supported different findings between type 1 and type 2 diabetic patients (61). Type 1 diabetes has long been associated with low BMD (7,39,61,62,63,64,65,66). However, data on the relationship between type 2 diabetes and BMD has not generated conclusive findings (61,63,65,66). Heterogeneity of study participants, patient populations studied, measurement and study techniques, and inappropriate control groups or absence of control groups may account for some of the inconclusive results previously reported (63,65). Some studies have found similar or higher BMD in type 2 diabetes compared to nondiabetic control subjects (2,61,63,64,65,67).

Differences in BMD levels between diabetic patients and controls have been attributed to several factors (Table 2). Lower BMD in type 1 diabetes versus type 2 diabetes could result from rapid bone loss after the onset of type 1 diabetes, reduced peak bone mass, increased bone loss preceding peak bone mass, or a common genotype that makes type 1 diabetics more susceptible to low BMD (61,68). Type 1 diabetics may experience high rates of bone turnover and resorption that may be attributed to secondary hyperparathyroidism, hypomagnesemia, and decreased levels of 1-25-hydroxycholecalciferol (10,15,40,69,70).

Table 2. BMD and Diabetes Mellitus

Type 1 Diabetes	Type 2 Diabetes
<ul style="list-style-type: none"> • Rapid bone loss after onset of diabetes • Reduced peak bone mass • Increased bone loss after attainment of peak bone mass • Common genotype lowering BMD • Lower BMD with increased duration of type1 diabetes • Menstrual disorders and/or early menopause may decrease BMD 	<ul style="list-style-type: none"> • Insulin resistance before onset of diabetes may improve BMD • High endogenous insulin may improve BMD • Lower BMD with increased duration of type 2 diabetes • Increased BMD in type 2 diabetics with excessive body weight

Elevated BMD levels observed in type 2 diabetics may be due to the period of insulin resistance before the onset of diabetes, which promotes hyperinsulinemia (63,66). High endogenous insulin levels may improve BMD (37). Hyperinsulinemia may also lead to increased BMD via its negative effect on sex hormone binding globulin (63). Furthermore, obesity has been associated with increased BMD (37). It may be that one possible reason for the association between obesity and BMD is due to the positive relationship between obesity and elevated endogenous insulin levels (37). Obesity has also been associated with increased BMD due to increased adipose tissues that produce estrogen (66,70). Bone turnover in type 2 diabetics with appropriate glycemic control has been reported to be equal to or lower than bone turnover in persons without diabetes. Consequently, some studies have reported higher bone mass in type 2 diabetics than in nondiabetic controls (70).

Insulin may act directly on bone tissue or insulin may work indirectly by binding to the insulin-like growth factor (IGF-1) receptor (63,65). In vitro studies

have demonstrated that insulin stimulates osteoblast cell proliferation involved in bone formation (37,65). Some cross-sectional studies have observed a positive association between BMD and insulin (37). In addition, the structural similarity between insulin and IGF-1 may play an important role in stimulating bone formation. IGF-1 is a polypeptide synthesized by bone cells and appears to regulate bone formation (35,37,38). Other cytokines and cellular messengers may also influence bone metabolism (63). Nonetheless, the duration of diabetes plays a critical role in increasing the risk of hip fracture given the lower BMD levels found among patients who have had diabetes for greater than 5 years (63).

Age of menarche and menopause plays a key role in bone formation and osteoporosis in women (71). Approximately 30% of type 1 diabetic women report amenorrhea, polymenorrhea, and oligomenorrhea throughout their reproductive years. This is double the prevalence of menstrual disorders observed among women without type 1 diabetes and, the differences are most pronounced when the onset of type 1 diabetes is prepubescent. Menstrual disorders may result in lower BMD (11,22). In addition, type 1 diabetes may promote early menopause causing lower BMD due to reduced levels of endogenous estrogen (71).

Estrogen replacement therapy has been shown to lower the risk of osteoporosis development (2,4,22,24,25,72). However, postmenopausal estrogen use may influence carbohydrate metabolism and may be associated with type 2 diabetes (73). Some studies have reported no increase in incidence of type 2 diabetes with postmenopausal estrogen use (67,68). Other studies reported by Zhang et al. (73) have shown that estrogen was associated with lower fasting glucose and insulin

levels, but estrogen's use was related to a rise in 2-hour insulin and glucose levels (73). Zhang et al. (73) suggested that postmenopausal estrogen use may relate to deterioration of glucose tolerance and that longer usage of postmenopausal estrogen among current users may increase the risk for type 2 diabetes (72). Wilson et al. (72) reported that laboratory research conducted on ovariectomized rats with reduced estrogen levels foster insulin resistance. Yet, estrogen treatment administered to the rats restored insulin sensitivity. Furthermore, juvenile rats undergoing estrogen withdrawal experienced augmented fasting and glucose stimulated insulin levels (72). Some studies have also reported that estrogen replacement therapy may be associated with less insulin resistance in postmenopausal women with type 2 diabetes (72). Yet, postmenopausal estrogen use may be more common among leaner women (57).

Hyperparathyroidism has been associated with decreased BMD (2,7). Grey et al. (58) showed that postmenopausal women with primary hyperparathyroidism were significantly heavier, had a greater total body fat mass, and had proportionately more android fat than age-matched, eucalcemic controls (58). After adjustment for body weight, there remained modest bone mass reductions in the postmenopausal women with primary hyperparathyroidism (58).

Primary hyperparathyroidism may lead to insulin resistance by promoting increased adiposity by selectively affecting skeletal muscle and not adipose tissue, thereby diverting carbohydrate to adipocytes (23,58). Insulin resistance may also occur due to the influence of the parathyroid hormone on adipocyte differentiation and function (58). Finally, insulin resistance may occur via the effects of obesity on calcium metabolism leading to secondary hyperparathyroidism (58,74). Obesity

increases the risk of developing type 2 diabetes (32,44,46,56,57). In addition, hyperparathyroidism has been associated with diabetes (75,76).

It has also been reported that bisphosphonates may increase BMD in type 2 diabetic persons via apoptosis of osteoclast cells, reduced osteoclastic recruitment, and inhibition of osteoclastogenesis resulting in decreased bone resorption (66). Chung et al. (66,77) suggested that HMG-CoA reductase inhibitors increase new bone formation in skeletal tissue by osteoblasts in both in vitro cell culture systems and in vivo mice experiments (66,77). A proposed mechanism for bone formation involves an increase in expression and synthesis of bone morphogenetic protein 2 that may play a role in fracture repair and bone regeneration (66,77).

Factors other than BMD may also impact hip fracture risk (Table 3). Diabetes is associated with increased disability in postmenopausal women (2,78). Physical disability, loss of independence, and diminished quality of life may increase hip fracture risk (78). Greater than 50% of older people with diabetes have reported some degree of physical disability (78). Functional disability may lead to further complications of diabetes including hyperglycemia, obesity, cardiovascular disease, peripheral vascular disease, depression, arthritis, and limited physical activity (78). It is possible that diabetic complications have a direct impact on hip fracture risk. Osteoporosis associated with type 1 diabetes and type 2 diabetes is worse in people with poor glycemic control (3,63,79). Poor glycemic control may result in hypercalciuria leading to negative calcium balance and secondary hyperparathyroidism. Consequently, bone resorption and bone loss may ensue (79).

Table 3. Diabetes Mellitus and Its Complications May Increase Hip Fracture Risk

Type 1 Diabetes	Type 2 Diabetes
<ul style="list-style-type: none"> • Physical disability • Loss of independence • Decreased quality of life • Hyperglycemia • Hypoglycemia • Cardiovascular disease • Peripheral vascular disease • Depression • Arthritis • Increased low-impact fall rates • Decreased neurological activity • Visual impairment • Poor glycemic control • Polyuria and nocturia • Hyperparathyroidism • Thyrotoxicosis 	<ul style="list-style-type: none"> • Physical activity • Loss of independence • Decreased quality of life • Hyperglycemia • Hypoglycemia • Cardiovascular disease • Peripheral vascular disease • Depression • Arthritis • Increased low-impact fall rates • Decreased neurological activity • Visual impairment • Poor glycemic control • Polyuria and nocturia • Hyperparathyroidism • Sedentary lifestyle

Thirty percent of the community-dwelling elderly population in developed countries fall at least once a year and 10-20% fall twice or more (29). The effect of elevated fall frequency and the fact that over 30% of elderly women have osteoporosis has led to increased rates of osteoporotic fractures with increasing age (29,80). Approximately 90% of hip fractures result from falling (14,80). Diabetic patients may be at increased risk of falls and consequently increased risk for hip fracture (2,29,39,81,82,83,84). Increased fall rates may be due to hypoglycemic episodes (84). Kennedy et al. (84) reported that diabetic patients treated with insulin therapy were at increased hip fracture risk possibly due to hypoglycemic mechanisms (84). Hypoglycemia can impair visual acuity, which may lead to increased fall incidence (7). Some studies have suggested that physical activity and certain regimens, such as weight-bearing activities, may reduce the risk for falling (2,28,29,30,32). Weight-bearing activity in older and frail persons improves muscle

strength and mobility (29,30). Yet, physical activity may increase risk for falls due to skeletal muscle movement that displaces the body's center of gravity (29). In particular, vigorous physical activity, especially in the elderly and those with functional disabilities, may yield the highest risk for fall-related fractures (31).

Physical activity has long been associated with increasing insulin sensitivity and decreasing abdominal adiposity and fat deposition (32). A sedentary lifestyle is considered a major risk factor for type 2 diabetes (7,32). Neurologic, vascular, and ophthalmic complications due to diabetes severity have also been shown to increase fall rates as well as hip fracture risk (7,84).

Diabetic retinopathy is the third leading cause of blindness (82). In addition, diabetes is the leading cause of adult blindness in the United States (43,44). Diabetic retinopathy leads to visual impairment and predisposition to falls and hip fractures (2,7,10,68,82). Yet, Ivers et al. (64) found that even after adjustment for visual impairment, their data concluded that there remained a significant association between diabetic retinopathy and hip fracture risk (64). The only proven prevention of diabetic retinopathy is strict glycemic control. Even then, about 12% of diabetics still develop retinopathy when following strict glycemic treatment (50). Diabetic related visual disability may increase noncompliance of diabetic patients to treatment regimen, difficulties in self-administration of insulin and oral pharmacological treatments, difficulties in glucose monitoring, and inability to self-screen for diabetic complications such as foot ulceration (82). Such problems, exacerbated by visual impairment, may have a profound impact on glucose control, disease burden, and consequently hip fracture risk. Ivers et al. (64) reported an increased risk of fracture

with diabetic retinopathy, advanced cataract, longer diabetes duration, and insulin treatment compliance (64). To complicate matters further, Schaumberg et al. (83) reported risk of cataract increased in persons with higher body mass indexes, taller persons, and persons with greater amounts of abdominal adiposity (83). Higher body mass indexes and greater amounts of abdominal adiposity are associated with development of type 2 diabetes (6,32,46,56).

There appears to be a relationship between duration of diabetes and poorer vision due to retinopathy and cataract formation (7,64,82). Fifty percent of Americans aged 65 to 74 years of age have some form of cataract (51). Cataract can lead to simulation affecting distance vision, glare related vision loss, and contrast difficulty (51). Thus, cataract development in diabetes persons may lead to increased fall rates due to vision impairment.

The EURODOAB Prospective Complications Study showed that retinopathy developed in 56% of diabetics within 7 years. Incidence of retinopathy peaked between 10 and 20 years of baseline diabetes duration (50). The impact of diabetic retinopathy on hip fracture risk may be more pronounced in diabetic patients with an early onset of the disease due to increased overall incidence of cataract and retinopathy (64,82).

Peripheral neuropathy frequently occurs in the diabetic population and is the leading cause of peripheral neuropathy in developed nations (2,84,85). Peripheral neuropathy increases foot ulceration and lesions (7,52,84,86). Not only does peripheral neuropathy increase foot ulceration and lesions, but also motor and sensory neuropathy predisposes the patient to infection (52). Consequently, infection may in

turn lead to further exacerbation of foot ulceration and lesions. Peripheral artery disease leads to increased risk of disability and physical functioning (78,79,86). Impaired physical functioning, in particular lower extremity functioning, leads to increased fall rates and hence, increased hip fracture risk. Peripheral neuropathy alters coordination and balance, resulting in reduced gait and decreased reflexes (2,68,80,81,86). Another complication that may be present when alterations occur in gait and balance is polyuria and nocturia, which may also increase the risk of falling (7). Some studies have also reported that peripheral artery disease in diabetics progresses at a faster rate than in nondiabetics with peripheral artery disease (84).

Two common endocrine problems in the diabetic population that may lead to osteoporosis include thyrotoxicosis and hyperparathyroidism (75,76). Thyrotoxicosis, namely Grave's disease, develops after the onset of diabetes in type 1 diabetic patients. The development of thyrotoxicosis increases with age and primarily occurs in postmenopausal women. Thyrotoxicosis has been suggested to be a cause of osteoporosis (75,76). Furthermore, persons with Grave's disease and type 1 diabetes have been reported to share a common *HLA* genotype (76). Hyperparathyroidism occurs with nearly the same frequency in type 1 as type 2 diabetics. Autoimmune hyperthyroidism is more common in type 1 diabetics and may be responsible for lower BMD in type 1 diabetic patients (76). Secondary hyperparathyroidism, hypomagnesaemia, and decreased levels of 1-25-hydroxycholecalciferol may increase bone turnover and bone resorption in type 1 diabetics (10,15,40,69,70).

One of the primary risk factors for type 2 diabetics is obesity (7,44,46,70).

Obese postmenopausal women have higher endogenous estrogen production and lower levels of sex hormone binding globulin that can increase BMD and lower hip fracture risk (11,65). Larger muscle in obese persons requires more work to move body mass, which may stimulate bone formation (11). Excess adipose tissue surrounding the femoral hip may serve as a protector in the act of a fall and therefore reduce the risk for hip fracture (11).

RESEARCH OBJECTIVE

The objective of this study was to establish a relationship between type 2 diabetes mellitus and osteoporotic hip fractures. Therefore, the hypothesis that was tested is that type 2 diabetes is associated with increased risk of osteoporotic hip fracture.

MATERIALS AND METHODS

Data Collection

The Utah Study of Nutrition and Bone Health (USNBH) is a case-control study conducted in Utah during 1991-2001 to determine risk factors for osteoporotic hip fracture. All study participants were determined from Utah residents aged 50-90 years. The average age was 76.36 (n=1779) for females and 74.21 (n=811) males, respectively. Age (within 5 years of cases) and sex matched controls, whom at baseline never had a hip fracture, were randomly selected from the Utah Drivers License pool if less than 65 years of age and the Medicare databases if greater than 65 years of age. Cases were obtained from 18 Utah hospital databases to validate hip fracture status. Interview-given questionnaires and picture-sort food frequency questionnaires were administered to participants in the study. All variables used in the statistical analysis were defined in the USNBH database obtained by the questionnaires administered to USNBH participants at the time of the study.

Potential variables included, but were not limited to, age, gender, weight, height, body mass index (weight in kg/height in m²), smoking status, estrogen use, alcohol status, physical activity, intake of certain vitamins and minerals, cognitive function, statin use, glucocorticoid steroids, economic status, education level, stroke, cardiovascular disease, and thyroid function. Based upon this information, independent variables were identified that could potentially affect the occurrence of hip fracture. Specific variables selected for analysis were sex, body mass index (BMI) calculated from participant reported weight and height, diabetes, smoking status,

alcohol usage, physical activity, education level, and estrogen use in women subjects only. Type 2 diabetes participants were classified by the age of onset of diabetes. Type 1 diabetes typically develops before 30-years-of-age (44,46). Therefore, the age of 30 was the cut off point for the classification of diabetes type. Greater than 30 years of age was used to distinguish type 2 diabetes. Type 1 patients were dropped from the study because of insufficient numbers for statistical analyses ($n=10$). Only the type 2 diabetic population was used in this study.

Potential participants with high impact trauma (considered a fall from greater than chair height or impact fractures sustained from vehicular accidents) and a low Mini-Mental State Examination (MMSE) score of less than or equal to 17 were excluded from the data set ($n=150$).

Statistical Analyses

Contingency tables were calculated and chi-square analysis was used to compare the expected contingency table to the observed contingency table. Logistic regression analysis and modeling techniques were used to determine the associations between type 2 diabetes and hip fracture risk. Initially odds ratios were used to evaluate the risk of hip fracture, and then the analyses were stratified by gender and BMI groups.

The dependent variable in the models was hip fracture which had two values, $\text{fract}=1$ (confirmed hip fracture) and $\text{fract}=0$ (no hip fracture). The dependent variable was binary (0 or 1). The independent variables were discrete in nature instead of continuous.

Because of the discrete nature of the data, the data was logit transformed and logistic regression analysis was used. The logistic regression model used in this study was:

$$\text{Ln}\{Y=[\text{Prob}(\text{fract}=1)]/[\text{Prob}(\text{Fract}=0)]\}=B_0+B_1*X_1+B_2*X_2+\dots+B_n*X_n$$

The X's were the independent variables. The B's were the logistic regression coefficients. Their estimates were represented by the b's. The B's represent the original unknown parameter, while b was its estimate.

The left-hand side of this relationship is known as the logit transformation of a probability. It is also called the log-odds ratio. The odds ratio gives the linear relationship between the dependant variable and the independent variable.

All of the variates used in the statistical modeling were defined in the Utah Study of Nutrition and Bone Health (USNBH) database obtained by from questionnaires administered to USNBH participants at the time of the study. All statistical analyses were conducted with SAS statistical software programs (SAS System Ver 8.02).

RESULTS

As depicted in Table 4, hip fracture was not associated with education levels ($p > 0.05$) in both genders. Physical activity decreased the risk of hip fracture for women ($p < 0.0001$) and for men ($p = 0.001$). Smoking status and alcohol use were associated with the occurrence of hip fracture in women, but the association was not significant in men. Estrogen use decreased hip fracture risk in women ($p < 0.0001$) in former or current users.

The risk of hip fracture was associated with type 2 diabetes. Among females, type 2 diabetes was more prevalent among cases vs. controls (15.6% vs. 11.7%; $p=0.02$). In the smaller number of men, the difference was similar (17.7% vs. 14.6%) but was not significant. The significant correlation was primarily found in females in which the risk of hip fracture increased accompanied with the onset of type 2 diabetes. As indicated by the odd-ratios listed in Tables 5 and 6, the values of the odds-ratios for either women or men were larger than one, indicating an increased risk of hip fracture in people with type 2 diabetes. However, in males, there was a wide range of variation for the odds-ratio, ranging from 0.9 to 2.0, which indicates that the association of type 2 diabetes with hip fracture was most likely stronger in females than in males, or that the smaller number of males resulted in lower statistical power to detect a significant association.

Considering BMI, hip fracture risk showed different patterns with respect to gender. In Table 7, females with a BMI larger than 30 had an odds-ratio of 2.0. Females with a BMI between 25 to 30 had an odds-ratio of 1.3. This indicated that

along with the increase of BMI, there was a significant association between hip fracture and type 2 diabetes and an increase in hip fracture risk. On the contrary, in Table 8, males with a BMI larger than 30 had the smallest odds-ratio of 0.8 compared with males of the other groups, BMI < 25 and BMI between 25 to 30 with odd-ratios of 1.2 and 1.7, respectively. Considering that a significant association between hip fracture risk and type 2 diabetes was not found in males, a higher BMI in males could have a protective effect against hip fracture.

Table 4. Demographic and Lifestyle Characteristics of Cases and Controls by Gender; The Utah Study of Nutrition and Bone Health; 1997-2001

	Women		Men	
	Cases* (N=882)	Controls* (N=897)	Cases* (N=350)	Controls* (N=461)
Age (mean in yrs, SD)	76.7 (9.1)	76.0 (9.4)	74.9 (9.5)	73.7 (10.7)
Weight (mean in kg, SD)	63.5 (14.1)	68.7 (14.5)	80.0 (14.8)	82.6 (15.2)
Height (mean in m, SD)	1.6 (0.1)	1.6 (0.1)	1.8 (0.1)	1.8 (0.1)
Body mass index (mean in kg/m ² , SD)	24.2 (5.1)	26.4 (5.1)	25.0 (4.1)	26.4 (4.3)
Education Level (N, %)				
< 12 years	460 (52.2)	454 (50.7)	161 (46.0)	204 (44.4)
≥ 12 year	422 (47.9)	442 (49.3)	189 (54.0)	256 (55.7)
Physical Activity Level** (N, %)				
None	220 (24.9)	111 (12.4)	45 (12.9)	41 (8.9)
One	241 (27.3)	186 (20.8)	111 (31.7)	101 (21.9)
Two	260 (29.5)	363 (40.5)	118 (33.7)	191 (41.4)
Three	161 (18.3)	236 (26.3)	76 (21.7)	128 (27.8)
	$p \leq 0.0001$		$p \leq 0.001$	
Smoking (N, %)				
Never	682 (77.5)	750 (83.6)	158 (45.1)	244 (2.9)
Former	138 (15.7)	123 (13.7)	154 (44.0)	179 (38.8)
Current	60 (6.8)	24 (2.7)	38 (10.9)	38 (8.2)
	$p \leq 0.0001$		$p \leq 0.075$	
Alcohol Drinker (N, %)				
Never	636 (72.4)	713 (79.7)	154 (44.1)	226 (49.1)
Former	133 (15.2)	81 (9.1)	114 (32.7)	128 (27.8)
Current	109 (12.4)	101 (11.3)	81 (23.2)	106 (23.0)
	$p \leq 0.0002$		$p \leq 0.27$	
Estrogen Use (N, %)				
Never	456 (53.0)	386 (43.7)		
Former	215 (25.0)	228 (25.8)		
Current	189 (22.0)	269 (30.5)		
	$p \leq 0.0001$			
Type 2 Diabetes (N, %)				
No	740 (84.4)	789 (88.3)	288 (82.3)	392 (85.4)
Yes	137 (15.6)	105 (11.7)	62 (17.7)	67 (14.6)
	$p \leq 0.02$		$p \leq 0.23$	

*Significant differences between cases and controls were established at $p \leq 0.05$, $p \leq 0.01$, and $p \leq 0.0001$.

**Physical Activity is categorized by use of heavy housework, yard work, or recreational activity. Never, one, two, and three are assigned levels based on engagement in exactly none, one, two, or all three types of physical activities.

Table 5. Risk of Hip Fracture Associated with Diabetes Status, Stratified by Gender, Unadjusted Analysis

Status of Type 2 Diabetes	Women			Men		
	Cases (N)	Controls (N)	Odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Odds ratio and 95% confidence interval
Type 2 Diabetic	137	105	1.4	62	67	1.3
Not Type 2 Diabetic	740	789	1.1 – 1.8	288	392	0.8 – 1.9

Table 6. Risk of Hip Fracture Associated with Diabetes Status, Stratified by Gender, Adjusted in Logistic Regression Models for Age, BMI, Physical Activity, Education Level, Estrogen Use in Women, Smoking, and Alcohol Use

Status of Type 2 Diabetes	Women			Men		
	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval
Type 2 Diabetic	137	105	1.7	62	67	1.4
Not Type 2 Diabetic	740	789	1.3 – 2.4	288	392	0.9 – 2.0

Table 7. Risk of Hip Fracture Associated with Diabetes Status for Women, Stratified by BMI; Adjusted in Logistic Regression Models for Age, Estrogen Use, Physical Activity, Education Level, Smoking, and Alcohol Use

Status of Type 2 Diabetes	BMI < 25 (Women only)			BMI 25 – 30 (Women only)			BMI > 30 (Women only)		
	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval
Type 2 Diabetic	49	25	1.5	44	37	1.3	37	40	2.0
Not Type 2 Diabetic	473	362	0.9 – 2.7	190	260	0.8 – 2.2	65	149	1.2 – 3.5

Table 8. Risk of Hip Fracture Associated with Diabetes Status for Men, Stratified by BMI; Adjusted in Logistic Regression Models for Age, Physical Activity, Education Level Smoking, and Alcohol Use

Status of Type 2 Diabetes	BMI < 25 (Men only)			BMI 25 – 30 (Men only)			BMI > 30 (Men only)		
	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval	Cases (N)	Controls (N)	Adjusted odds ratio and 95% confidence interval
Type 2 Diabetic	27	21	1.2	26	24	1.7	9	21	0.8
Not Type 2 Diabetic	150	161	0.6 – 2.2	102	172	0.9 – 3.2	31	57	0.3 – 2.1

DISCUSSION

This study supports the hypothesis that the risk of hip fracture is significantly associated with type 2 diabetes. The significant association was found primarily in females. This may be due to the higher number of female participants with type 2 diabetes and not a consequence of gender. However, the odds-ratios for both male and females was greater than one, which indicates that type 2 diabetics are at increased risk for hip fracture. Yet, the odds-ratio trends still indicate a stronger risk for type 2 diabetic females. These findings are in agreement with Nicodemus et al. (70) who reported that type 2 diabetic women have increased hip fracture risk compared to non-diabetic women (70). On the contrary, it has been reported that type 2 diabetic women have a lower frequency of sustaining a hip fracture (65). Furthermore, Forsen et al. (60) found that type 2 diabetic women with a long duration of the disease were at increased risk for hip fracture. However, type 2 diabetic men with a shorter duration of the disease were found to have an increase hip fracture risk (60).

The findings also support previous research that physical activity decreases risk for hip fracture. Sedentary living is a strong risk factor for bone loss and fractures (2,7,10,22). Physical activity, in particular bone building exercises, help to maintain or possible increase BMD and thereby reduce fracture risk (29,30). Epidemiological studies have suggested that hip fracture risk decreases by 20% to 50% for physically active adults compared to sedentary adults in the United States (31). Even after achieving peak bone mass, bone tissue can adapt to mechanical loading promoting

bone remodeling. If physical activity is absent, then reduction in bone mass often ensues (30,31). Other possible benefits of physical activity may include improved agility and coordination, as well as increased muscle strength that may lower the likelihood of experiencing a fall, and therefore reducing fracture risk (2,29,30,32).

Estrogen use in former and current female users was significantly associated with decreased hip fracture risk. Estrogen deficiency due to menopause accelerates bone loss (2,4,24,25). BMD losses of 2-4% occur up to five to ten years after menopause in the absence of estrogen replacement therapy (2).

Smoking status and alcohol usage were significantly associated with hip fracture risk in women but no such association was found in men. This may be due to the small sample size of male participants. Some studies have reported lower BMD and increased risk of fractures with cigarette smoking (2,10). Excessive alcohol intake is a strong risk factor for bone loss and fractures (2,15). Increased risk of fractures may also be due to loss of physical ability (2,10). Excessive alcohol intake may lead to protein and/or calcium malnutrition, reduced mobility, and hypogonadism (5). Chronic alcohol use increases fracture risk due to falls and hepatic disease (2). Hepatic encephalopathy, resulting in decreased cognitive ability, may lead to increased fall rates as a result of decreased functionality and cognition.

Table 7 demonstrates that in female participants, that along with increased BMI, there was a significant association between hip fracture and type 2 diabetes. Two of the primary risk factors for type 2 diabetes are obesity and sedentary living (7,44,45,46,70). Greater than 8 out of 10 persons with type 2 diabetes are considered overweight (46). The higher the proportion of fatty tissue in the body, the greater the

resistance to insulin in muscle and tissue cells (46,58). It may be that proper glucose control minimizes diabetic complications and is more correlated with body weight and physical activity levels. In addition, persons with type 2 diabetes can improve serum glucose levels by moderate weight loss (46). Therefore, increased body weight and sedentary living may contribute to poor glycemic control, diabetic complications and physical disability (2,78). Physical disability, loss of independence, and diminished quality of life may increase hip fracture risk (78). Functional disability may lead to further complications of diabetes including hyperglycemia, obesity, cardiovascular disease, peripheral vascular disease, depression, arthritis, and limited physical activity (78). It is possible that diabetic complications have a direct impact on hip fracture risk. Osteoporosis associated with diabetes is worse in people with poor glycemic control (3,63,79). Poor glycemic control may result in hypercalciuria leading to negative calcium balance and secondary hyperparathyroidism. Consequently, bone resorption and bone loss may ensue (79). Diabetic complications increase hip fracture risk either directly or indirectly. Poor glycemic control can also lead to hypoglycemic episodes resulting in increased fall rates and increased hip fracture risk (2,27,76). Poor glycemic control also impacts visual acuity and can cause diabetic retinopathy thereby increasing the likelihood of falling (2,10,63,77).

Table 8 indicates that male participants with high BMIs may have some protection against hip fractures for type 2 diabetics however; caution should be taken because statistical significance was not found. Adipose tissue surrounding the femoral hip may provide a protective cushion in the event of a fall (2,21,22).

Moreover, it has been suggested that the most consistent predictor of BMD is total body fat (22,23). Greater total body fat results in elevated BMD.

Of greater importance to future research is the fact that this study showed that type 2 diabetes is a risk factor for hip fracture, supporting the hypothesis of this research that type 2 diabetes increases risk for hip fracture. However, the case-control design of this study cannot be used to unequivocally state that type 2 diabetes causes hip fracture. Rather, this study establishes that there is a strong association between hip fracture risk and type 2 diabetes. Type 2 diabetes is multifactorial and many underlying factors contribute to the development of type 2 diabetes. Many of these factors could pose a risk for hip fracture.

SUMMARY

Osteoporotic hip fractures severely affect quality of life by diminishing functional capacity to perform routine activities (1,2,7). Critical prevention to delay, or eliminate susceptibility to hip fracture, must focus on high-risk populations and administering proper treatment (7). The diabetic population may be at high-risk for hip fractures due to the multifactorial nature of diabetes mellitus and osteoporosis (3,13). The focus of this study was to perform a statistical analysis on various data collected in the Utah Study of Nutrition and Bone Health (USNBH) to determine whether there was an association between type 2 diabetes and hip fracture, which was the case based upon the analysis of the data in this study. Therefore, the hypothesis that type 2 diabetes is associated with increased risk of osteoporotic hip fracture is acceptable. The results and conclusions derived from the data may eventually lead to better therapy for treating and/or minimizing hip fracture incidence.

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